PRACTALL Consensus Report

Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/ American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report

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There are remarkable differences in the diagnostic and therapeutic management of atopic dermatitis practiced by dermatologists and pediatricians in different countries. Therefore, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology nominated expert teams who were given the task of finding a consensus to serve as a guideline for clinical practice in Europe as well as in North America. The consensus report is part of the PRACTALL initiative, which is endorsed by both academies. (J Allergy Clin Immunol 2006;118:152-69.)

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Abbreviations used
AD: Atopic dermatitis
APT: Atopy patch test
CyA: Cyclosporine A
DC: Dendritic cell
IDEC: Inflammatory dendritic epidermal cell
LC: Langerhans cell
MnSOD: Manganese superoxide dismutase
pDC: Plasmacytoid dendritic cell
SPT: Skin prick test
TCI: Topical calcineurin inhibitors
T_{Reg}: T regulatory

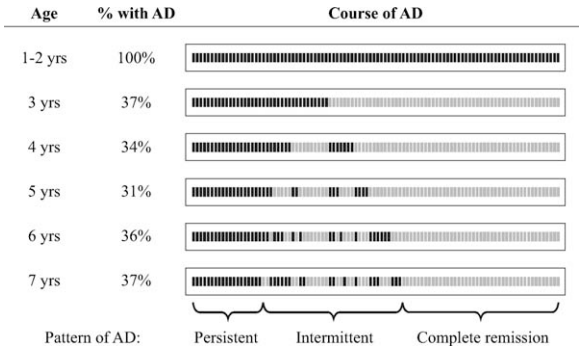


FIG 1. The natural history of AD from infancy to childhood obtained from the prospective birth cohort study Multicenter Atopy Study.[3]

Atopic dermatitis (AD) is a chronic inflammatory pruritic skin disease that affects a large number of children and adults in industrialized countries. The 12-month prevalence in 11-year-old children, as studied in the Global International Study of Asthma and Allergies in Childhood trial, ranged from 1% to 20%, with the highest prevalence typically found in Northern Europe.[1]

In 45% of children, the onset of AD occurs during the first 6 months of life, during the first year of life in 60%, and before the age of 5 years in at least 85% of affected individuals.[2] In those children with onset before the age of 2 years, 20% will have persisting manifestations of the disease, and an additional 17% will have intermittent symptoms by the age of 7 years (Fig 1).[3] In adults with AD, only 16.8% had onset after adolescence.[4,5]

The clinical pattern of AD varies with age. Infants typically present with erythematous papules and vesicles on the cheeks, forehead, or scalp, which are intensely pruritic. The childhood phase typically occurs from 2 years of age to puberty. Children are less likely to have the exudative lesions of infancy and instead exhibit more lichenified papules and plaques representing the more chronic disease and involving the hands, feet, wrists, ankles, and antecubital and popliteal regions. The adult phase of AD begins at puberty and frequently continues into adulthood. Predominant areas of involvement include the flexural folds, the face and neck, the upper arms and back, and the dorsa of the hands, feet, fingers, and toes. The eruption is characterized by dry, scaling erythematous papules and plaques and the formation of large lichenified plaques from lesional chronicity.

GENETIC AND OTHER RISK FACTORS FOR AD

Parental atopy, in particular AD, is significantly associated with the manifestation and severity of early AD in children. The circumstance by which the genetics of AD might play a role in the level of natural history and development has been reflected in 2 forms of genetic studies:

- genome-wide screens that identify broad regions of the genome linked with AD and
- candidate gene studies that examine a presumed contribution of genetic variants of disease-process genes in case-control association studies.

Both approaches highlight the search for disease-specific AD alleles, as well as identifying overlapping genes associated with other allergic characteristics and disorders. This process has been recently reviewed.[6] A European study of about 200 families with affected sibs looked at phenotypes for AD, as well as allergic sensitization, and found a region of highest linkage at human chromosome 3q21.[7] Another study of 148 nuclear families in which AD, as well as other intermediate phenotypes, including asthma phenotype and total serum IgE level, were examined identified association with 5 regions, including 1q21, 17q25, 20p, 16q, and 5q31.[8] A Swedish study of 197 affected sib pairs identified 4 phenotypes, as well as 11 locations, associated with all of the different phenotypes that ranged from severity of AD, specific IgE, and direct diagnosis of AD.[9] Finally, a Danish study looked at a small number of affected sib pairs and found association with 3 locations within the genome.[10] Not all of these locations are highly robust, and most of these associations from genome-wide screens might not yield effective identification of specific genes when examined in more detail; these are summarized in Table I.[7-10] Table II[11-13] summarizes the findings of candidate gene studies and their association with atopy and asthma.

Among nongenetic determinants for the development of AD, the role of infantile feeding has been investigated.[14] A recent meta-analysis suggests that the incidence of infantile AD is reduced by breast-feeding for a least 4 months,[15] but this effect is most probably transient and tends to disappear after 3 years of age.

Environmental factors also play a role in the development of AD. In contrast to asthma, the role of passive tobacco smoke exposure in AD is inconclusive. However, exposure to aeroallergens (pets, mites, and pollen) has been clearly shown to increase the risk factors for AD and AD severity.[16-18] In addition, aeroallergens are a trigger for exacerbations in adult AD. Sensitization to food allergens (cow's milk and hen's eggs) is associated with infantile AD and related to disease severity. Food allergen sensitization is also predictive for persistence of

TABLE I. Genome-wide screens of AD

Reference	Study population	Sample	Phenotypes	Regions of highest linkage
Lee et al,[7] 2000	European	199 families with 2 affected siblings	AD	3q21
			Allergic sensitization	3q21
Cookson et al,[8] 2001	British	148 nuclear families recruited through children with active AD	AD	1q21
				17q25
			AD plus asthma	20p
			Serum IgE	16q-tel
				5q31
Bradley et al,[9] 2002	Swedish	109 families (197 affected full sib pairs, 9 affected half sib pairs)	AD	3p24-22
				5p13
				6q16
				10p13-12
			AD plus specific IgE	18q21
				4q24-26
				6p
				1p32
			Extreme AD	18p
				21q21
				7p14
			Severity score of AD	13q14
				15q14-15
				17q21
				3q14
Haagerup et al,[10] 2004	Danish	23 affected sib-pair families	AD plus specific IgE	3p26-24
				4p15-14
				18q11-12

symptoms throughout childhood.[3] Only in a minority of those with food sensitization (up to 33% of patients with moderate-to-severe disease of all age groups) are food allergens of clinical relevance, as demonstrated by food challenge studies.[19] Another risk factor for persistent AD symptoms is the severity of disease in infancy.

Children with AD are at high risk of allergic asthma and allergic rhinitis. Of those with AD during the first 2 years of life, 50% will have asthma during subsequent years.[20] The severity of AD, including early sensitization to food, increases the risk of asthma and allergic rhinitis.[3,21] The exact mechanism for the progression of the disease in children with AD is unknown; however, it appears to be a complex interaction of genetics, environmental exposure, and sensitization. For children with a family history of atopy, early AD, and sensitization, almost all are expected to have asthma.

In murine models of AD, epicutaneous sensitization leads to systemic allergic responses, increased IgE levels, airway eosinophilia, airway sensitization, and airway hyperresponsiveness similar to that seen in human asthma and allergy.[22] In human subjects a recent report suggests that in selected individuals sensitization to peanut allergen might occur through the skin.[23]

IMMUNOPATHOLOGY

The pathophysiology of AD is the product of a complex interaction between various susceptibility genes, host environments, infectious agents, defects in skin barrier function, and immunologic responses.[24] Activation of T lymphocytes, dendritic cells (DCs), macrophages, keratinocytes, mast cells, and eosinophils are characteristic of AD skin inflammatory responses.

Histopathology

Clinically unaffected skin in AD is not normal. It is frequently dry and has a greater irritant skin response than normal healthy skin. Microscopic studies reveal a sparse perivascular T-cell infiltrate in unaffected AD skin that is not seen in normal healthy skin (Fig 2).[25]

Acute AD skin lesions present to the physician as intensely pruritic, erythematous papules associated with excoriation and serous exudation. There is a marked infiltration of $CD4^+$ activated memory T cells in acute AD. Antigen-presenting cells (eg, Langerhans cells [LCs], inflammatory dendritic epidermal cells [IDECs], and macrophages) in lesional and, to a lesser extent, in nonlesional

TABLE II. Candidate gene studies in AD

Gene	Gene name	Location	Variant	Phenotype	Population	Association
TLR2	Toll-like receptor 2	4q32	Arg753Gln	Severe AD	German	Yes
				AD	German	No
IRF2	Interferon regulatory factor 2	4q35	−467 G/A	AD	Japanese	Yes
CSF2	Colony-stimulating factor 2	5q31	−677 A/C	AD	British	Yes
			3606 T/C, 3928 C/T	AD at 12 and 24 mo	Canadian	Yes
IL4	IL-4	5q31	−590 C/T	AD	Japanese	Yes
				Extrinsic AD	German	Yes
				AD	Australian	No
				Intrinsic AD	Japanese	No
IL13	IL-13	5q31	Arg130Gln	AD	Canadian	Yes
				AD	Japanese	Yes
				AD	German	Yes
			−111 C/T	AD	Dutch	Yes
				AD	Japanese	No
IL5	IL-5	5q31	−703 C/T	Blood eosinophilia in AD	Japanese	
IL18[11]	IL-18	11q22	−137 G/C, −133 C/G 113 T/G, 127 G/T	AD	German	Yes
CARD4[12]	Caspase recruitment domain-containing protein 4	7p14-p15-	rs2736726	AD	German	Yes
			rs2075817			
			rs2975632			
			rs2075822			
			rs2907749			
			rs2907748			
CD14	Monocyte differentiation antigen CD14	5q31	−159 C/T	AD (interaction with dog ownership)	American	Yes
				AD	German	No
IL12B	IL-12B	5q31-33	1188 A/C	AD, psoriasis	Japanese	Yes
SPINK5	Serine protease inhibitor, Kazal-type 5		Glu420Lys	AD	British	Yes
				AD	Japanese	Yes
				AD	Japanese	Yes
				Asthma with AD	German	Yes
				Disease severity and food allergy in AD	Japanese	Yes
FCER1B	High-affinity IgE receptor β chain	11q13	RsaIin2, RsaIex7	AD	British	Yes
GSTP1	Glutathione-S-transferase, PI	11q13	Ile105Val	AD	Russian	Yes
			Haplotypes	AD	Russian	Yes
PHF11	Plant homeodomain zinc finger 11 protein	13q14	T/C intron3, G/A 3 UTR	Childhood AD	Australian	Yes
CMA1	Mast cell chymase	14q11	BstXI	AD	Japanese	Yes
				AD	Japanese	Yes
				AD	Japanese	No
				AD	Italian	No
			−1903 G/A	IgE levels in AD	British	Yes
				AD	German[13]	Yes
IL4RA	IL-4 Receptor chain	16p12	Gln551Arg	Severe AD	American	Yes
				Adult AD	Japanese	Yes
				Ad (interaction with infection)	British	Yes
				Intrinsic AD	Japanese	No

TABLE II. (continued)

Gene	Gene name	Location	Variant	Phenotype	Population	Association
			−3223 C/T	Extrinsic AD	German	Yes
				AD	Japanese	Yes
CARD15	Caspase recruitment domain-containing protein 15	16q12	2722 G/C	AD	German	Yes
				AD	German[11]	Yes
RANTES	Regulated on activation, normally T cell expressed plus secreted	17q11-q12	−403 A/G	AD	German	Yes
				AD	Hungarian	No
EOTAXIN	Eotaxin	17q21	−426 C/T, −384 A/G	IgE levels in AD	Japanese	Yes
TGFβ1	TGF-β1	19q13.1	Arg25Pro	AD	British	Yes
SCCE	Stratum corneum chymotryptic enzyme	19q13	AACCins	AD	British	Yes

skin bear IgE molecules.[26] Mast cell degranulation can be observed.

Chronic AD skin lesions have undergone tissue remodeling caused by chronic inflammation. These skin lesions are associated with thickened plaques with increased skin markings (lichenification), increased collagen deposition in the dermis, and dry fibrotic papules. Macrophages dominate the dermal mononuclear cell infiltrate. Eosinophils also contribute to the inflammatory response, and T cells remain present, although in smaller numbers than seen in acute AD.

Cytokines and chemokines

AD skin lesions are orchestrated by the local tissue expression of proinflammatory cytokines and chemokines.[27] Cytokines, such as TNF-α and IL-1 from resident cells (keratinocytes, mast cells, and DCs), binds to receptors on the vascular endothelium, activating cellular signaling, including the nuclear factor (NF) κB pathway, and inducing expression of vascular endothelial cell adhesion molecules. These events initiate the process of tethering, activation, and adhesion to the endothelium, followed by extravasation of inflammatory cells. Once the inflammatory cells have infiltrated into the tissue, they respond to chemotactic gradients established by chemoattractant cytokines and chemokines, which emanate from sites of injury or infection. These molecules play a central role in defining the nature of the inflammatory infiltrate in AD.

The onset of acute AD is strongly associated with the production of T_H2-produced cytokines, notably IL-4 and IL-13, levels of which are significantly higher in AD individuals compared with control subjects.[28] Mediating isotype switching to IgE synthesis and upregulating expression of adhesion molecules on endothelial cells, IL-4 and IL-13 are implicated in the initial phase of tissue inflammation, whereas the T_H2 cytokine IL-5, which is involved in eosinophil development and survival, predominates in the chronic form of the disease.[28] Increased production of GM-CSF in patients with AD is reported to inhibit apoptosis of monocytes, thereby contributing to the chronicity of this condition.[29] The maintenance of chronic AD also involves production of the T_H1-like cytokines IL-12 and IL-18, as well as several remodeling-associated cytokines, such as IL-11 and TGF-β1, which are expressed preferentially in chronic forms of the disease.[30]

Increased expression of C-C chemokines (monocyte chemoattractant protein 4, eotaxin, and RANTES) contributes to infiltration of macrophages, eosinophils, and T cells into acute and chronic AD skin lesions.[31] Cutaneous T cell–attracting chemokine (CCL27) is highly upregulated in AD and preferentially attracts cutaneous lymphocyte antigen–positive T cells into the skin. Finally, selective recruitment of CCR4-expressing T_H2 cells is mediated by macrophage-derived chemokine and thymus and activation-regulated cytokine, levels of which are increased in patients with AD.[27] Severity of AD has been linked to magnitude of thymus and activation-regulated cytokine levels.[32] In addition, chemokines, such as fractalkine,[33] IFN-γ–inducible protein 10, monokine induced by IFN-γ, and IFN-γ–inducible α chemoattractant, are strongly upregulated in keratinocytes[34] and contribute to T_H1 cell migration toward the epidermis.

IgE and IgE receptors

In about 80% of adult patients with AD, the disease is associated with increased serum IgE levels (>150 kU/L), sensitization against aeroallergens and food allergens, and/or concomitant allergic rhinitis and asthma.[35,36] In contrast, 20% of adult patients with AD have normal serum IgE levels. This subtype of AD often has a late onset (>20 years of life) and a lack of IgE sensitization against inhalant or food allergens.[35,36] However, some of these patients might have IgE sensitization against microbial antigens, such as *Staphylococcus aureus* enterotoxins and *Candida albicans* or *Malassezia sympodialis* (formally known as *Pityrosporum ovale*).[37,38] In addition,

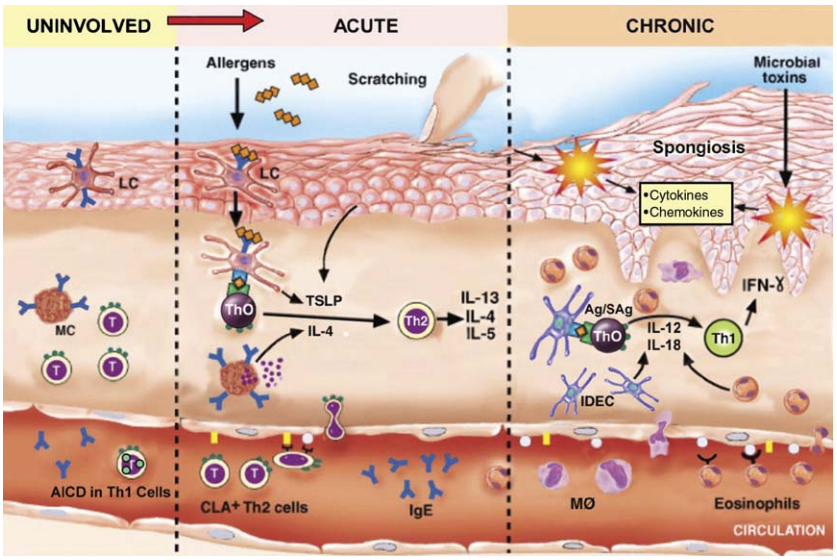


FIG 2. Immunologic pathway involved in the progression of AD. Updated from Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol 2000;105:860-76. *LC,* Langerhans cell; *MC,* mast cell; *TSLP,* human thymic stromal lymphopoietin; *Ag,* antigen; *SAg,* superantigen; *AICD,* activation-induced cell death; *CLA,* cutaneous lymphocyte antigen; *MO,* monocyte.

some of these patients have positive reactions on the atopy patch test (APT).[39] In children a transient form of AD with low IgE serum levels and without any detectable sensitizations has been shown, which develops into the extrinsic variant of AD with increasing IgE serum levels and developing sensitizations against aeroallergens and food allergens later in life.[40]

Expression of IgE receptors (ie, the high-affinity receptor for IgE [FcεRI]) can be found in the epidermal skin lesions of patients with AD. The reason for a higher IgE-binding capacity of DCs in the skin and in the peripheral blood of patients with AD is that FcεRI is regulated distinctly on DCs of atopic and nonatopic subjects.[41]

Skin barrier dysfunction

AD is characterized by dry skin, even involving nonlesional skin and increased transepidermal water loss. In particular, ceramides serve as the major water-retaining molecules in the extracellular space of the cornified envelope, and the barrier function of these complex structures is provided by a matrix of structural proteins, which are bound to ceramides.[42,43] A reduced content of ceramides has been reported in the cornified envelope of both lesional and nonlesional skin in patients with AD. Changes in stratum corneum pH levels have been found in patients with AD and might impair lipid metabolism in the skin.[44] Overexpression of stratum corneum chymotryptic enzyme is also likely to contribute to the breakdown of the AD epidermal barrier.[45] This would allow penetration of irritants and allergens, which trigger an inflammatory response, thus contributing to the cutaneous hyperreactivity characteristic of AD. The increased susceptibility to irritants in patients with AD might therefore represent a primary defect of epidermal differentiation compounded by the presence of inflammation-induced skin damage.

Key cells in AD

T cells. The key role of immune effector T cells in AD is supported by the observation that primary T-cell immunodeficiency disorders frequently have increased serum IgE levels and eczematous skin lesions, which clear after successful bone marrow transplantation.[24,46] In animal models of AD, the eczematous rash does not occur in the absence of T cells.[47] In addition, treatment with topical calcineurin inhibitors (TCIs), which specifically target activated T cells, significantly reduces the clinical skin rash present in AD.[48]

The important role that T_H1 and T_H2 cytokines play in the skin's inflammatory response has been demonstrated in experimental models of allergen-induced allergic skin inflammation in mice with targeted deletions or overexpression of these cytokines. In this regard transgenic mice genetically engineered to overexpress IL-4 in their skin have inflammatory pruritic skin lesions similar to those seen in patients with AD, suggesting that local skin expression of T_H2 cytokines plays a critical role in AD.[49] Allergen-sensitized skin from IL-5–deficient mice has been found to have no detectable eosinophils and exhibits decreased thickening, whereas skin from IL-4–deficient mice displays normal thickening of the skin layers but has a reduction in eosinophil counts.[47] In patients with AD, activated T cells with skin-homing properties, which express high levels of IFN-γ, predominantly undergo apoptosis in the circulation, skewing the immune response to surviving T_H2 cells as a mechanism for T_H2 predominance.[50] In the affected skin these T cells switch

on effector cytokines and induce the activation and apoptosis of keratinocytes.[51]

Recently, T regulatory (T_{Reg}) cells have been described as a further subtype of T cells, with immunosuppressive function and cytokine profiles distinct from those of either T_H1 or T_H2 cells.[52-54] T_{Reg} cells are able to inhibit the development of both T_H1 and T_H2 responses. Mutations in a nuclear factor expressed in T_{Reg} cells, Foxp3, result in immune dysregulation polyendocrinopathy enteropathy X-linked syndrome characterized by hyper-IgE, food allergy, and eczema.[55] In addition, staphylococcal superantigens subvert T_{Reg} cell function and might thereby augment skin inflammation.[56]

DCs. Two types of FcεRI-bearing myeloid DCs have been found in the lesional skin of patients with atopic eczema, namely LCs and IDECs. Both display a different function in the pathophysiologic network of AD. LCs play a predominant role in the initiation of the allergic immune response and prime naive T cells into T cells of the T_H2 type with high IL-4–producing capacity, which predominate in the initial phase of AD.[57] Further on, stimulation of FcεRI on the surface of LCs by allergens induces the release of chemotactic signals and recruitment of precursor cells of IDECs and T cells *in vitro*. Stimulation of FcγRI on IDECs leads to the release of high amounts of proinflammatory signals, which contribute to the amplification of the allergic immune response.

In contrast to other inflammatory skin diseases, such as allergic contact dermatitis or psoriasis vulgaris, only very low numbers of plasmacytoid DCs (pDCs), which play a major role in the defense against viral infections, can be detected within the epidermal skin lesions of AD.[58] pDCs in the peripheral blood of patients with AD have been shown to bear the trimeric variant of FcεRI on their cell surface, which is occupied with IgE molecules. The modified immune function of pDCs in patients with AD after FcεRI-mediated allergen stimulation might contribute to the deficiency of pDCs in patients with AD to produce type I IFNs and thereby contribute to the high susceptibility of patients with AD toward viral skin infections, such as herpes simplex–induced eczema herpeticum.[59]

Keratinocytes. Keratinocytes play a role in innate immunity by expressing Toll-like receptors and producing antimicrobial peptides in response to invading microbes.[60] AD keratinocytes secrete a unique profile of chemokines and cytokines after exposure to proinflammatory cytokines. This includes high levels of RANTES after stimulation with TNF-α and IFN-γ.[61] They are also an important source of thymic stromal lymphopoietin, which activates DCs to prime naive T cells to produce IL-4 and IL-13.[62]

There is growing evidence to incriminate the epidermis as both target and enhancer of the inflammatory response in AD.[34,63] Apoptosis of keratinocytes induced by T cells and mediated by Fas is a crucial event in the formation of eczema/spongiosis in AD.[63] IFN-γ released from T cells upregulates Fas and several cytokines, such as IL-1α, IL-1 receptor agonist, TNF-α, and GM-CSF, and chemokines on keratinocytes.[34,64] There is evidence that cleavage of E-cadherin and sustained desmosomal cadherin contacts between keratinocytes that are undergoing apoptosis result in spongioform morphology in the epidermis as a hallmark of eczematous lesions.[65] Suppression of keratinocyte activation and apoptosis remains a potential target for the treatment of AD.[34,62,66]

Eosinophils. Studies over the past 2 decades have shown that eosinophils play a major role in AD, characterized by activated eosinophils in the peripheral blood and in the lesional skin.[67,68] Interestingly, psychosocial stress represents an important trigger for the increase of eosinophil counts in the peripheral blood.[69] Inhibition of eosinophil apoptosis in AD, probably mediated by an autocrine release of IL-5 and GM-CSF, appears to be a relevant mechanism for the eosinophil accumulation observed in AD.[70] Several lines of investigation indicate that eosinophils are recruited to, and activated at, tissue sites by T_H2 cytokines, such as IL-5 and IL-13.[68] In addition, chemokines (eotaxin and RANTES) also contribute to eosinophil chemotaxis and activation. Moreover, interaction of eosinophil surface molecules and the endothelial cells vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 are important for eosinophil extravasation and activation. Eosinophils might also play a role in switching the T_H1 response in AD through production of significant amounts of IL-12 on activation.[71] Once activated, the eosinophil is capable of releasing an armory of potent cytotoxic granule proteins and chemical mediators contributing to tissue inflammation, as shown by the deposition of eosinophil products in the inflamed skin.[67,68] Moreover, eosinophils might have a relevant role in neuroimmunologic interactions.[72]

Pathophysiology of pruritus in AD

Patients with AD have a reduced threshold for pruritus manifested as cutaneous hyperreactivity and scratching after exposure to allergens, changes in humidity, excessive sweating, and low concentrations of irritants.[73] Although pruritus can occur throughout the day, it is usually worse at night, frequently disrupting the patient's sleep and overall quality of life.[74] The mechanisms of pruritus in AD are complex and poorly understood. Allergen-induced release of histamine from skin mast cells is not an exclusive cause of pruritus in AD because antihistamines are not effective in controlling the itch of AD unless there is associated urticaria.[75] The observation that TCIs and corticosteroids are effective therapeutic agents at reducing pruritus suggests that the inflammatory cells play an important role in driving pruritus.[76,77] Other substances that have been implicated in pruritus include cytokines, neuropeptides, proteases, eicosanoids, and eosinophil-derived proteins.[78-81]

Triggers of AD

Stress. Stress-induced immunomodulation is altered in patients with AD, but the exact mechanisms are not well understood.[69] This phenomenon might be mediated by neuroimmunologic factors, such as neuropeptides, which can be found in the blood and within the epidermal nerve fibers in close association with epidermal LCs. Increased levels of nerve growth factor and substance P can be

found in the plasma of patients with AD and correlate positively with the disease activity.[82] Enhanced levels of brain-derived growth factor can be detected in the sera and plasma of patients with AD. Brain-derived growth factor has been shown to reduce eosinophil apoptosis while enhancing chemotaxis of eosinophils *in vitro*.[72]

Allergens. Placebo-controlled food challenge studies have demonstrated that food allergens can induce eczematoid skin rashes in a subset of infants and children with AD.[83,84] In some patients urticarial reactions can trigger the itch-scratch cycle that flares this skin condition. Children with food allergy have positive immediate skin test responses or serum IgE directed to various foods, particularly egg, milk, wheat, soy, and peanut. Food allergen–specific T cells have been cloned from the skin lesions of patients with AD, providing direct evidence that foods can contribute to skin immune responses. In addition, it is well established that food can exacerbate AD both through allergic and nonallergic hypersensitivity reactions. Furthermore, direct contact with the skin (eg, in the preparation of meals or when feeding infants) might be an important factor for the aggravation of eczema.

Beyond the age of 3 years, food allergy is frequently outgrown, but sensitization to inhalant allergens is common. Pruritus and skin lesions can develop after intranasal or bronchial inhalation challenge with aeroallergens in patients with AD. Epicutaneous application of aeroallergens (eg, house dust mites, weeds, animal danders, and molds) by means of the APT on uninvolved skin of patients with AD elicits eczematoid reactions in a subset of patients with AD.[85] A combination of effective house dust mite reduction measures has been reported to improve AD. The isolation from AD skin lesions and allergen patch test sites of T cells that selectively respond to *Dermatophagoides pteronyssinus* (Der p 1) and other aeroallergens supports the concept that immune responses in AD skin can be elicited by inhalant allergens.

Microorganisms. Most patients with AD are colonized with *S aureus* and experience exacerbation of their skin disease after infection with this organism.[86] In patients with AD with bacterial infection, treatment with antistaphylococcal antibiotics can result in reduction of skin disease. An important strategy by which *S aureus* exacerbates AD is by secreting toxins called superantigens, which stimulate activation of T cells and macrophages. Most patients with AD make specific IgE antibodies directed against staphylococcal superantigens, which correlate with skin disease severity.[87] Superantigens also induce corticosteroid resistance, thereby complicating their response to therapy.[88]

Binding of *S aureus* to skin is enhanced by AD skin inflammation. This is supported by clinical studies demonstrating that treatment with topical corticosteroids or tacrolimus reduces *S aureus* counts in AD. AD skin has also been found to be deficient in antimicrobial peptides needed for host defense against bacteria, fungi, and viruses.[89,90] This constellation of genes is underexpressed because of the significant upregulation of T_H2 cytokines in AD. Along with lower levels of proinflammatory cytokines, such as TNF-α and IFN-γ, the decrease in antimicrobial defenses within patients with AD might explain their increased susceptibility to skin infections compared with that seen in patients with psoriasis.[90]

Patients with AD have an increased propensity toward disseminated infections with herpes simplex or vaccinia virus. Susceptibility to severe viral infections, such as eczema herpeticum or eczema vaccinatum, might be linked to the severity of atopy.[91] As such, smallpox vaccination is contraindicated in patients with AD unless there is imminent danger of exposure to smallpox.[92]

There is increasing evidence that the opportunistic yeast *Malassezia* species represents a contributing factor in AD.[37,93] Several studies have demonstrated the presence of specific serum IgE, a positive skin prick test (SPT) response, and a positive APT response against *Malassezia* species in adults with AD.[37] IgE sensitization to *Malassezia* species is specific for patients with AD but is not seen in patients with asthma or allergic rhinitis.[94,95]

Autoantigens. Autoreactivity of patients with AD to human proteins might contribute to the pathophysiology of this condition.[96,97] IgE against autoantigens could stimulate type 1 hypersensitivity reactions and DCs and induce the proliferation of autoreactive T cells.[98] Recently, it has been shown that IgE against manganese superoxide dismutase (MnSOD) from the skin-colonizing yeast *M sympodialis* cross-reacts with human MnSOD.[99] Because patients reacting to human MnSOD were sensitized against the *M sympodialis* MnSOD, sensitization most likely occurs primarily by exposure to the environmental fungal MnSOD.

Irritant factors. Frequently, rough or woolly clothing leads to mechanical irritation and exacerbation of AD and eczema. Chemical irritants like skin-cleansing agents should also be considered but can only be satisfactorily identified by means of avoidance.

DIAGNOSIS

Symptoms and signs and diagnostic criteria

The use of well-defined diagnostic criteria is important in the diagnosis of AD, especially for those patients who lack the typical phenotype of the disease, and the diagnostic criteria developed by Hanifin and Rajka are widely accepted (Fig 3).[100] Other criteria have been developed[101] that correlate well with those of Hanifin and Rajka, although use of only visible eczema as a criterion might lead to overdiagnosis of the disease. Skin biopsies are not essential for the diagnosis but might be required to exclude other diagnoses, particularly in adults.

Differential diagnosis

The most important differential diagnoses are other forms of eczema. Especially in adulthood, combination forms are prevalent with components of atopic, contact, and irritative eczema. Atopic eczema of the hands and feet must be differentiated from psoriasis in the palms and soles and from tinea. Scabies infection must always be considered. The differential diagnosis of acute AD with

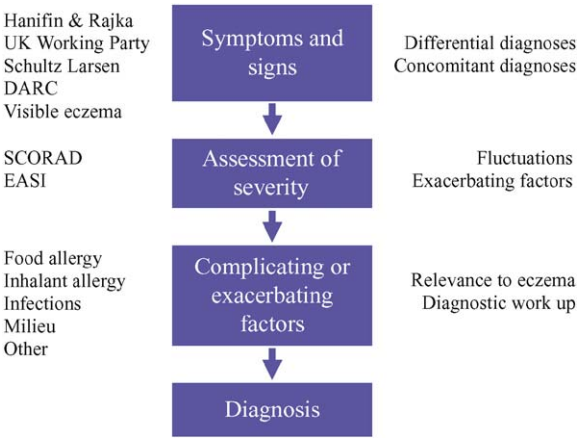


FIG 3. Diagnostic approach to patients presenting with symptoms and signs of atopic dermatitis.

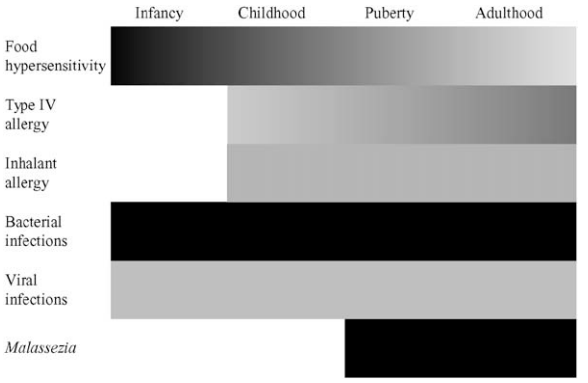


FIG 4. Relative significance of complicating or exacerbating factors in patients with AD from infancy to adulthood.

intense erythema of the skin, together with exudation or blistering, for example, differs from differential diagnoses of the chronic lichenified forms. Other, more rare diseases should be suspected, especially in recalcitrant cases: in children genodermatoses, such as Netherton syndrome, including the recently described immune dysregulation polyendocrinopathy enteropathy X-linked syndrome,[102] should be considered, and in both children and adults vitamin deficiencies and malignancies, especially cutaneous T cell lymphoma/mycosis fungoides, should be considered.

Diagnostic work-up

The investigation of exacerbating factors in AD involves a patient history, specific skin and blood tests, and challenge tests, depending on the degree of the disease severity and on the suspected factors involved (Fig 4).

Food

There is no universally recommended diet for patients with AD. Dietary restrictions should only be recommended in cases of an established diagnosis of food hypersensitivity. International guidelines for the diagnosis of food hypersensitivity have been published.[83,103] As regards food-induced eczema, it is important to note that the predictive value of a positive case history is lower than that for food-induced immediate reactions.[104]

Both SPTs and measurement of specific IgE can be used to assess for sensitization to a food at any age. Diagnostic sensitivity and specificity varies considerably among different foods, reading systems, and age groups. A decision point discriminating between clinical relevance of sensitization (with challenge as the gold standard) has been developed with regard to specific IgE and SPTs to egg, milk, peanut, and others foods in children.[105-107] Decision points can be helpful in making the decision to perform oral challenges. However, the need for challenges has to be decided on an individual basis.

Other invalidated tests, such as lymphocyte cytotoxicity tests, the basophil degranulation test, or measurement of serum IgG (or subclasses), should not be used.

APT is primarily a tool to investigate the mechanisms of eczema in the skin. However, APT can also reveal sensitization in patients with AD and might identify a subgroup of such patients. An elimination diet should not be recommended for a patient solely on the basis of a positive APT response to a food.[108]

All the abovementioned tests require specialist knowledge in their performance and interpretation.

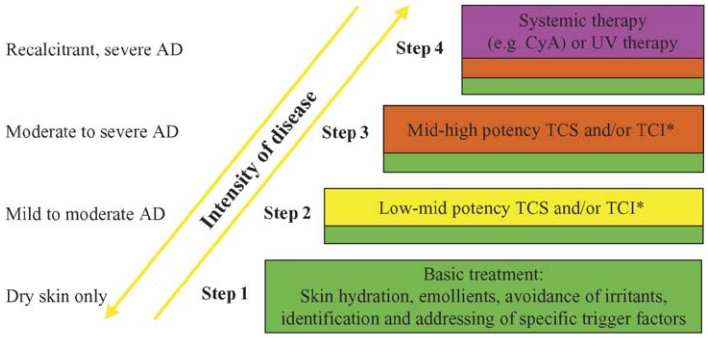
Standardized, physician-supervised food challenges provide the most accurate diagnostic tool.[103] However, it should be noted that patients can present with reactions at least 24 hours after a food challenge, and the challenge settings and protocol should be appropriately designed; for example, in case of a negative challenge response, the skin of the patient should be examined the following day.[104] After a diagnosis has been established, a tailor-made education program for the patient should be initiated.

Inhalant allergy

Sensitization to inhalant allergens is often seen in patients with AD. Allergens can exacerbate AD either by means of inhalation, direct contact with the skin, or ingestion. Sensitization can be detected by means of SPTs (if the skin is free from eczema) or by measurement of specific IgE antibodies. In addition, APTs can be used to assess the response in the skin. Most important allergens include dust mite, animal dander, and pollen confirmed by clinical trials and avoidance measures. The role of dust mite allergen exposure is supported by patch tests, avoidance studies, and the very high titers of IgE antibodies to mite proteins in a large proportion of adults, as well as children older than 7 years with AD.[94,109-111] The positive effect of house dust mite avoidance with special encasings has been shown in various studies.[110]

Contact allergy

In patients with AD, contact sensitization to topical medications frequently occurs, especially in adults. In cases of worsening eczema despite treatment, the possibility of contact dermatitis needs to be ruled out by means of patch testing. Patients with AD are no more likely to be sensitized than normal.



TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A
* Over the age of 2 years

FIG 5. Stepwise management of patients with AD.

SYSTEMIC AND TOPICAL TREATMENT

The management of AD presents a clinical challenge.

Basic treatment

Basic therapy of AD should comprise optimal skin care, addressing the skin barrier defect with regular use of emollients and skin hydration, along with identification and avoidance of specific and nonspecific trigger factors. Nonspecific irritants include contactants, such as clothing made from occluding or irritating synthetic or wool material.[112] Further irritating factors are soaps and hot water temperature during showering or bathing. Contacts with water should be minimized, moderately heated water should be used, and mild syndets with an adjusted pH value (acidified to pH 5.5-6.0 in order to protect the acid mantle of the skin) should be used for cleansing.[113] Other specific provocation factors and airborne and food allergens have to be considered (see the section on diagnosis for how to identify allergens).[108,114]

Further treatment, on the basis of disease severity, includes the addition of multiple therapeutic agents in a step-wise fashion (Fig 5). A combination of different topical agents might be indicated. In cases of severe AD that cannot be controlled with topical treatment, systemic treatment options might need to be considered. For optimal disease management, regular medical supervision, together with education of the patient or care providers and appropriate psychosocial support, is needed. In selected patients hospitalization might be of great benefit, especially in centers with a multidisciplinary team approach.

Topical treatment

Emollients. A key feature of AD is severe dryness of the skin caused by a dysfunction of the skin barrier with increased transepidermal water loss.[115] This is typically accompanied by intense pruritus and inflammation. The regular use of emollients is important for addressing this problem, and together with skin hydration, it represents the mainstay of the general management of AD.[116,117] Emollients should be applied continuously, even if no actual inflammatory skin lesions are obvious.[118] Because different emollients are available, selection criteria, such as the individual skin status, seasonal and climatic conditions, and the time of day, should be considered for optimizing the patients' basic treatment. ''Water-in-oil'' or ''oil-in-water'' emulsions might be substituted to support the skin barrier function. Emollients containing polidocanol are effective in reducing pruritic symptoms. Adjuvant application of topical preparations with urea allows for intensive hydration of the skin, whereas salicyl acid can be added to an emollient for the treatment of chronic hyperkeratotic lesions.[119]

Topical glucocorticosteroids. Topical glucocorticosteroids are still an important tool for the treatment of acute flare-ups.[120,121] Over recent years, the risk of adverse effects induced by topical steroids could effectively be reduced by optimizing application protocols and using new steroid preparations with improved risk/benefit ratios and lower atrophogenic potential, such as prednicarbate, mometasone furoate, fluticasone, and methylprednisolone aceponate.[77,122,123] For the topical use of glucocorticosteroids, different therapeutic schemes have been established: intermittent use might be as effective as an initial therapy with a high potent steroid followed by a time-dependent dose reduction or change over to a lower potent preparation.[124] The choice of an adequate vehicle is important to achieve the optimal therapeutic effect. Recent data indicate that in children and adults an application of corticosteroids (fluticasone) on unaffected skin twice weekly prevents further flare-ups of AD.[125] Aside from an anti-inflammatory effect, treatment with topical steroids contributes to a reduction of skin colonization with *S aureus* and therefore might affect a further trigger factor of AD.[126,127]

The side effects of uncontrolled topical steroid use, particularly on delicate skin areas, are well documented, and therefore topical steroid preparations should be applied no more than twice daily as short-term therapy for acute eczematous lesions. Only mild to moderately potent preparations should be used on genital, facial, or intertriginous skin areas. In children only mild to moderately potent steroid preparations should be used.[128]

In general, during acute flares, steroids should be used in combination with baseline emollient skin care to avoid steroid overuse and steroid-related side effects.

TCIs. The TCIs pimecrolimus and tacrolimus allow a steroid-free, anti-inflammatory topical therapy of AD. In both animal and human studies, both molecules demonstrated an immunomodulatory activity.[129] In the United States and Europe pimecrolimus cream (1%) and tacrolimus ointment (0.03%) are approved for the treatment of AD in children aged 2 years and older[130] and in adults.[131] Tacrolimus ointment (0.1%) is only approved for use in adults.

The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with moderate potency,[132] whereas 1% pimecrolimus cream is less active.[133] Thus far, no trials have been published comparing pimecrolimus 1% with a mild corticosteroid. Both agents proved to be effective, with a good safety profile for a treatment period of up to 2 years with pimecrolimus[134] and up to 4 years with tacrolimus.[135]

A frequently observed side effect with TCIs is a transient burning sensation of the skin. In a comparative study of the local side effects of 0.03% tacrolimus ointment versus 1% pimecrolimus cream in children, pimecrolimus achieved better local tolerability than tacrolimus.[136]

Preliminary studies indicate that treatment with TCIs is not associated with a risk of skin atrophy.[137] Therefore they are a useful alternative for the treatment of sensitive skin areas, such as the face and intertriginous regions.

Generalized viral infections, such as eczema herpeticum or eczema molluscatum, have been observed during TCI treatment.[138] It is unclear whether a trend for increased frequency of viral superinfections with use of TCIs really exists.[134]

Although there is no evidence of a causal link of cancer and the use of TCIs, the United States Food and Drug Administration has issued a black-box warning for pimecrolimus (Elidel; Novartis, Basel, Switzerland) and tacrolimus (Protopic; Astellas, Deerfield, Ill) because of a lack of long-term safety data.[139,140] Furthermore, the new labeling states that these drugs are recommended as second-line treatments and that their use in children younger than 2 years of age is currently not recommended. Long-term safety studies with TCIs in patients with AD, including infants and children, are ongoing.[134]

Wet-wrap therapy. A wet layer of cotton dressing, which is then covered with tubular bandages applied over emollients[141] in combination with antiseptics or topical steroids,[142] has been shown to be beneficial in cases of exacerbated AD skin lesions.[143] A more practical alternative approach using clothing rather than bandages has also been described in detail.[144]

Topical antimicrobial therapy. The skin of patients with AD is heavily colonized with *S aureus*, even at uninvolved sites. Toxins secreted by the majority of *S aureus* on the skin behave as superantigens and, as discussed in the pathophysiology section, can directly influence the disease activity, although clinical signs of bacterial superinfection might be absent.[145,146] Topical antiseptics, such as triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether) or chlorhexidine, offer the advantage of a low sensitizing potential and low resistance rate. They can be used in emollients or as part of an additional wet-wrap dressing therapy.[146] The topical use of triclosan has been shown to be effective in significantly reducing skin colonization with *S aureus* and skin symptoms.[147] An irritative, photoallergenic, phototoxic, mutagenic, or carcinogenic potential of triclosan has not been observed.[148] The use of silver-coated textiles and silk fabric with a durable antimicrobial finish can reduce *S aureus* colonization and eczema severity.[149,150] These new options are still under investigation.

The addition of a topical antimicrobial agent to a topical steroid preparation has been shown to result in greater clinical improvement than a topical steroid alone.[151] Interestingly, AD seems not to be associated with a higher risk of sensitization against topical antimicrobials.[152]

Because of deficient skin barrier function, patients with AD are exposed to a higher risk of recurrent bacterial superinfections of the skin. For the treatment of mild and localized forms of this secondary infection, a topical antibiotic treatment might be beneficial.

Although erythromycin and fusidic acid have been widely used in Europe, high resistance rates of *S aureus* to erythromycin have resulted in a preferential use of fusidic acid.[153] Topical fusidic acid has proved to be very effective against *S aureus* because of its low minimal inhibitory concentration and good tissue penetration.[154] However, long-term therapy with fusidic acid is suspected to be responsible for increasing resistance.[155] Therefore a restricted topical application for only short periods of about 2 weeks is advisable.[156] For intranasal eradication of methicillin-resistant *S aureus*, topical mupirocin has been shown to be effective.[157]

Other secondary infections caused by yeasts, dermatophytes, or streptococci have also been implicated as trigger factors in AD.[158] In general, signs of secondary infections should only be treated if present.

SYSTEMIC TREATMENT

Antimicrobial treatment

Systemic antibiotic treatment is indicated for widespread bacterial secondary infection, (primarily *S aureus*). First- or second-generation cephalosporins or semisynthetic penicillins for 7 to 10 days are usually effective. Erythromycin-resistant organisms are fairly common, making macrolides less useful alternatives.[159] In cases of penicillin or cephalosporin allergy, clindamycin or oral fusidic acid are possible alternatives. Unfortunately, recolonization after a course of antistaphylococcal therapy occurs rapidly.[160] Maintenance antibiotic therapy, however, should be avoided because it might result in colonization by methicillin-resistant organisms.

Infection of the skin with the herpes simplex virus in the form of an eczema herpeticum (Kaposi's varicelliform eruption) represents a severe and possibly life-threatening complication of AD, requiring a systemic antiviral treatment with acyclovir or other antiviral agents (eg, valacyclovir).[138]

Recent findings underline the pathogenetic importance of a fungal colonization as a trigger factor.[37,96,99] Contradictory data have been published about the efficacy of a systemic treatment of AD with ketoconazole,[161,162] and although it is assumed that selected patients with AD might benefit from a topical or systemic antimycotic therapy,[163] the effect of a therapeutic intervention needs to be better defined by further studies.

Systemic corticosteroids

Although oral corticosteroids are commonly used for many different skin diseases, few randomized clinical trials have been performed in patients with AD thus far.[164] It is well known that relapse after the discontinuation of oral steroids is often observed. Corticosteroids in the form of a long-term oral therapy are associated with a series of well-documented side effects (eg, disturbance of growth, osteoporosis, cataracts, and development of lymphopenia). In cases of acute flare-up, patients might benefit from a short course of systemic therapy with corticosteroids, but long-term use and use in children should be avoided.

Cyclosporin A

As with TCIs, cyclosporin A (CyA) inhibits calcineurin-dependent pathways, resulting in reduced levels of proinflammatory cytokines, such as IL-2 and IFN-γ. Multiple clinical trials have shown CyA to be an effective treatment for adult and childhood AD, and although relapse after discontinuation of therapy is often observed, posttreatment disease severity often does not return to baseline levels.[165-167]

Despite the effectiveness of oral CyA in the treatment of AD, because of the possible side effects, particularly renal toxicity, the use of CyA should be limited to patients with severe refractory disease, contraindications must be excluded, and blood pressure and laboratory parameters must be monitored closely. The treatment can be performed in the form of a short- or long-term therapy with high-dose (3-5 mg/kg/d) or low-dose (2.5 mg/kg/d) administration, depending on the patients' individual medical conditions.[168,169] The principle of treatment should be to aim for the lowest effective dose and the shortest treatment period because toxicity is related to both of these factors. In children it should be considered that vaccinations might not be effective during immunosuppression.

Azathioprine

Azathioprine is a long-known systemic immunosuppressive agent affecting purine nucleotide synthesis and metabolism, which has been shown to be efficient for many dermatologic conditions.[170] It is also used quite frequently as monotherapy in nonlicensed indications, including AD.[171] Although most reports on the use of azathioprine in AD have been uncontrolled, open, and retrospective studies, there is accumulating evidence for its efficacy in severe recalcitrant AD.[172-174] Azathioprine has a number of side effects, including myelosuppression, hepatotoxicity, gastrointestinal disturbances, increased susceptibility for infections, and possible development of skin cancer. Because azathioprine is metabolized by the thiopurine methyltransferase, a deficiency of this enzyme should be excluded before starting oral immunosuppression with azathioprine.[174] The recommended dosage of azathioprine for dermatologic indications is 1 to 3 mg/kg daily but should be determined based on thiopurine methyltransferase levels.[175] Regular blood tests must be performed throughout treatment with azathioprine.[173] The onset of action is usually slow, and benefit might not be apparent until 2 to 3 months after starting treatment.[176]

Antihistamines

The therapeutic value of antihistamines seems to reside principally in their sedative properties, and they are useful as a short-term adjuvant to topical treatment during relapses associated with severe pruritus. Nonsedating antihistamines seem to have only very modest value in atopic eczema.[177,178] Although there are no large controlled studies to date, newer nonsedating antihistamines seem to have little or no value in atopic eczema.[177]

Phototherapy

The treatment of AD with phototherapy is well established and represents a standard second-line treatment for adults.[179] In phases of acute flares, a combination with corticosteroids is often practiced.

The following therapy options can be used for AD: broad-band UVB (280-320 nm), narrow-band UVB (311-313 nm), UVA (320-400 nm), UVA1 (340-400 nm), PUVA, and Balneo-PUVA. In addition, combinations of UVB and topical glucocorticosteroids and UVB with UVA, as well as UVA1 medium- and high-dose therapy, showed favorable results.[180-182]

In children UV therapy should be restricted to adolescents older than 12 years, except in exceptional cases. It must be emphasized that to date, information about the long-term side effects of UV therapy is still not available.

Immunotherapy

To date, hyposensitization is not an established instrument for the treatment of AD. Although a number of case reports suggest clinical benefit from allergen-specific desensitization in AD, double-blinded controlled trials have failed to show consistent efficacy of immunotherapy in the treatment of AD.[183] A recent randomized multicenter trial investigated the efficacy of an allergen-specific immunotherapy of house dust mite preparations in patients with AD sensitized to house dust mite allergens for 1 year and revealed a dose-dependent effect on disease symptoms.[184] However, further well-controlled studies are needed to determine the future role of immunotherapy for AD.

Additional treatment options and future perspectives

The development of new, targeted therapeutic approaches is based on an increasing knowledge of the cellular and molecular aspects in atopic diseases. Most of the new approaches aim at inhibiting components of the

allergic inflammatory response, including cytokine modulation (eg, TNF inhibitors),[185,186] blockade of inflammatory cell recruitment (chemokine receptor antagonists and cutaneous lymphocyte antigen inhibitors),[187] and inhibition of T-cell activation (alefacept and efalizumab).[86]

EDUCATION

The goal of the patients' education should be living with atopic dermatitis by means of an empowered patient or, in the case of infants and young children, a caregiver who can work as a partner with the doctor in self-managing their own or their children's disease.

Education to enhance disease knowledge, psychologic improvement in disease perception, and scratch control behavior modification, together with regular daily treatment, will lead to better skin care. This improvement in disease control will restore family dynamics, and the patient and family will cope better and have an overall improvement in quality of life. Additionally, education should be aimed at reducing doctor shopping, facilitating a better partnership between the doctor and the patient-parent, and decreasing the long-term costs of chronic disease treatment.

Many preliminary studies have been single nurse-led interventions that were usually not controlled to assess outcomes.[188] From the recent controlled studies, there is the general impression that positive outcomes are dependant on the time spent with parents and the qualification of the trainer.[189-191] Sharing personal experiences in managing AD was helpful in 80% of those parents attending the program conducted by Staab et al.[192]

A 12-lesson educational program[192] described positive outcomes after 1 year, including diminished fear of topical corticosteroid cream use. In a recent German multicenter study 820 children with AD were randomized into an intervention group (n = 443) and a control group (n = 377).[193] The intervention group underwent a 12-hour education program on an outpatient basis. After 1 year, the overall Severity Score for Atopic Dermatitis (SCORAD) measure, quality of life, scratching index, and adherence to treatment showed statistically significant improvement.

Fundamentally, each patient with AD should be educated on various aspects of the disease. For economic and practical reasons, structured education will target patients with moderate and severe chronic AD and their parents. Structured patient education should enable both the patient and the parent to have realistic short-term goals, enter a process of problem solving, accept living with their disease, appropriately use available social support, and enhance their own motivation for therapy.

POTENTIAL APPROACHES FOR PRIMARY AND SECONDARY PREVENTION OF AD

Based on the idea of diet as modulatory, a number of controlled interventions have tested this hypothesis of primary prevention through the nutritional route. Hydrolyzed cow's milk formula consists of predigested peptides of whey and casein. The formulas have equivalent nutritional values but a reduced capacity to induce IgE-mediated reactions.[194-197] A large controlled study in high-risk infants using different partially and extensively hydrolyzed formulas for the first 6 months of life demonstrated that extensively hydrolyzed casein formula has the capacity to reduce AD by 50% in the first year of life.[198,199] A different approach for primary prevention is suggested by the introduction of probiotics (*Lactobacillus* GG) into the maternal and infantile diet. One study reported a decreased incidence of AD but had no effect on allergic sensitization.[200] Elimination diets in the mother are not recommended because of their limited success. Other potential avenues that are being explored include adding bacterial, mycobacterial, and parasitic materials into the infant diet.

A secondary prevention trial with cetirizine for infants with AD and a positive family history of asthma failed to demonstrate an effect for the whole group. In a subset of patients with dust mite or grass pollen sensitization, the incidence of asthma was reduced by 50%.[20] This concept is currently being investigated in a second trial of 500 children.[20] Trials using environmental control measures have shown potential effects in AD severity in children, although not in adults.[16] Another secondary prevention trial is under investigation based on the early treatment of AD with topical pimecrolimus to prevent the progression of AD to asthma based on the concept that the skin is the primary site of sensitization.

This document represents a consensus of an international panel of experts from the European Academy of Allergology and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. These common proposals were developed to aid in the diagnosis and treatment of AD on both sides of the Atlantic.

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